REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

The Examiner is thanked for the courtesies extended with the telephone call of July 17, 2007. The Examiner is also thanked for entering the Information Disclosure Statement filed on February 6, 2007, and for granting the benefit date of September 12, 2000. The Examiner is further thanked for withdrawing the rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 112, first paragraph.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 28-46 are currently under consideration. Claim 29 is canceled and claims 28 and 31-33 are amended without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that the claims herewith are patentably distinct over the prior art, and these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims presented herein are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply to clarify the scope of protection to which Applicants are entitled.

Support for the amended claims can be found throughout the specification as originally filed. For instance, amended claims 28 and 32 can be found, for example, on page 4, line 25 - page 5, line 9, on page 7, lines 9-13, and on page 28, lines 2-7.

II. REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH IS OVERCOME

Claims 28 and 30-34 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Office Action contends that although the scope of claims 28 and 30-34 is smaller than previously claimed, the scope of the amended claims is still much greater than the

specification provides. The Office Action also asserts that written description is based on whether Applicants were in possession of the claimed invention, and that the specification, namely paragraph [209], does not discuss the use of Bifidobacterium other than Bifidobacterium longum.

Although Applicants do not agree with the Office Action, in the interest of expediting prosecution, claim 28 has been amended to introduce the subject matter of claim 29 into claim 28. The instant invention herein relates to a microorganism of the genus Bifidobacterium transformed with a cloning vector having promoters and terminators of HU gene of a microorganism of the genus Bifidobacterium. According to the Office Action, evaluation of the specification's compliance with the written description requirement should be determined by whether the specification as filed describes the claimed invention in a manner such that a person skilled in the art would recognize that the Inventors were in possession of the claimed invention, i.e., "microorganism of the genus Bifidobacterium transformed with a cloning vector having promoters and terminators of HU gene of a microorganism of the genus Bifidobacterium."

With this in mind, Applicants assert that a person skilled in the art would recognize that the Inventors were in possession of the claimed invention. The specification describes that "an introduced gene can be efficiently expressed by using expression vector containing a promoter and a terminator involved in expressing a gene coding for a histone-like DNA-binding protein (abbreviated herein after to HU protein) (Biochimie, 72; 207-212 (1990)) inherently highly expressed in the bacteria belonging to the genus Bifidobacterium" (specification, page 5, lines 2-9). This disclosure supports amended claim 28.

At the time of filing of the instant application, it was known in the art that HU protein function includes transcription, transposition, and replication. For instance, Drlica et al. (Microbiol Rev 51: 301-319, 1987) relates to HU protein function and indicates that "[o]ne potential function of HU involves transcription" (page 311, left column, lines 17-18), although "HU is also involved in three types of site-specific recombination in which proper orientation and positioning of nucleotide sequences are important"(page 311, right column, line 15-17) and "HU also affects in vitro assays for initiation of DNA replication" (page 312, left column, lines 1-2). Goshima et al (Biochimie, 72: 207-212, 1990) mentions that "[the HU protein] has been thought to be a structural component of bacterial nucleoides," and that "HU protein is important in intercellular processes such as replicative transposition of bacteriophage Mu," "ori2-

dependent DNA replication of mini-F plasmids," and "site-specific DNA inversion of Hin, Gin, Pin and Shafflon systems" (page 207, left column, lines 1-10). Goshima additionally indicates that "HU protein has been well conserved during evolution of prokaryotes" (page 207, left column, lines 11-12). Furthermore, Sayre et al. (J Bacteriol 172: 4672-4681, 1990) indicates that "Type II DNA-binding proteins (also called HU proteins) are ubiquitous in bacteria" (page 4672, left column, lines 1-2). Accordingly, it is clear that a person skilled in the art at the time of filing would recognize that HU gene is a very important gene for bacteria, and that a microorganism of the genus Bifidobacterium has a HU gene.

The specification as filed exemplifies promoters and terminators of HU gene of Bifidobacterium longum for a method of isolating promoters and terminators of HU gene, and a method for introducing into a cloning vector (specification, page 25, line 7 – page 27, lines 12, and Example 3). Clearly, the Inventors were in possession of separating promoters and terminators of HU gene from a microorganism of the genus Bifidobacterium, and introducing them into a cloning vector.

In addition, a person skilled in the art could readily understand from Argnani et al (Microbiol 142: 109-114, 1996; submitted in IDS of June 16, 2005) that Plasmid pDG7, E.coli-Bifidobacterium shuttle vector, which is similar to a cloning vector of the instant application, can be used for transforming a microorganism of the genus Bifidobacterium other than B. longum.

As Applicants have stated previously, the presently claimed invention is also supported by Li et al. (Cancer Gene Therapy 10:105-111, 2003; submitted in IDS of June 28, 2006), published after the instant application, that a bacterium of the genus Bifidobacterium other than Bifidobacterium Longum can be used. Li et al uses the instant invention with Bidifocaterium adolescentis, a bacterium of the genus Bifidobacterium other than Bifidobacterium longum. This is clear from that Li et al. cites Yazawa (Cancer Gene Ther. 7:269-274, 2000; cited in IDS of June 16, 2005), and thus, it is clear that Li et al has used the instant invention according to the knowledge of Yazawa.

Moreover, Applicants also provide the deposit information of other Bifidobacterium strains (see, e.g., specification, page 16, lines 22-25), thereby providing additional examples of Bifidobacterium in addition to B. longum.

Therefore, a person skilled in the art could readily conceive from the specification as filed and from the state of the art at the time of filing that the Inventors are clearly in possession

of the claimed invention and, notably, could readily understand that the scope of the instant invention (amended claim 28) encompasses not only B. longum, but a microorganism of the genus Bifidobacterium.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 first paragraph is respectfully requested.

III. REJECTIONS UNDER 35 U.S.C. § 103(a) ARE OVERCOME

Claims 28-46 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yazawa (Proceedings of the American Association for Cancer Research Annual Meeting 40: 88, 1999; hereinafter "Yazawa") in view of Brown et al. (U.S. Patent No. 6,416,754B1; hereinafter "Brown"). Applicants respectfully traverse this rejection.

The specification of the instant application recites: "However, these bacteria have pathogenicity in humans and are thus not always safe gene delivery vectors in gene therapy of solid tumors. Actually, some reports have demonstrated febrile adverse reactions as side effects after injection with Clostridium butyricum spores or oral intake of Salmonella typhi (Eur. J. Cancer. 3: 37-41 (1967), J. Clin. Invest. 90: 412-420 (1992), Infect. Immun. 60: 536-541 (1992))." Thus, it is clear that it has been reported in 1992 that Clostridium is not always safe as a gene delivery vector in gene therapy of solid tumors, which is before the filing date of Brown (March 3, 1994).

Brown relates to a method of gene delivery involving sporulation, which recites "Antitumor activity is optimally produced by spores rather than the vegetative form (Mose and Mose, supra), and C. Actobutylicum produces spores under the conditions present in the targeted tumor. (Brown et al.; [0147])" (column 5, line 19029), and it has been clarified that antitumor activity is "optimally produced by spores rather than the vegetative form."

This sporulation method is also described in Examples 1, 2, and 4 of Brown. Brown's recitation that the spore form is the optimal embodiment teaches away from the vegetative form of bacteria used in the instant invention. Further, even it is a similar anaerobic bacterium, there is a possibility that spores transfers at random to normal tissues, and spore differs significantly from vegetative form.

In Example 2, Brown uses spores of Clostridium after killing vegetative forms by heat shocking at 80°C for 20 min before administration. On the other hand, the instant invention

relates to a bacterium belonging to the genus Bifidobacterium. As the bacterium belonging to the genus Bifidobacterium is not a spore-forming bacterium, the instant invention uses, naturally, a vegetative form. Compared to a vegetative form, spores have a higher resistance to physical and chemical treatments including heating or germicide, and it is relatively easy to administrate in the actual treatment, manufacturing pharmaceutical compositions, and to store; there is no need to be sensitive.

On the contrary, vegetative form has a very low resistance to physical and chemical treatments including heating or germicides. As a bacterium belonging to the genus Bifidobacterium is absolutely anaerobic, it is very difficult to administrate in the actual treatment, manufacturing pharmaceutical compositions, and to store, which requires lot of attention.

Therefore, there is no possibility for a motivation to combine the invention of Brown using spores of Clostridium, and the invention of Yazawa using vegetative form of a bacterium belonging to the genus Bifidobacterium. In case there is one, it is merely to consider using vegetative form of the bacterium belonging to the genus Bifidobacterium which is safe, instead of using spores of Clostridium having a problem of safety.

Regarding the above, there is the following description in the instant specification (see, e.g., ¶12, 13 and 17 of the specification as published):

> "In recent years, however, a system for the convenient and reproducible genetic transformation of stains of the genus Bifidobacterium was developed (Microbiology, 142: 109-114 (1996); Biosci. Biotechnol. Biocem. 61: 1211-1212 (1997))."
>
> "However, the development of regulatory sequences including a promoter for highly expressing an introduced gene was still not satisfactory."
>
> "Further, the present inventors examined a system of genetically transforming the bacteria belonging to the genus Bifidobacterium, and as a result, they found that an introduced gene can be efficiently expressed by using expression vector containing a promoter and a terminator involved in expressing a gene coding for a histone-like DNA-binding protein inherently highly expressed in the bacteria belonging to the genus Bifidobacterium, particularly in Bifidobacterium longum."

And in Example 3, a method for constructing plasmid pBLHU15 having a promoter and terminator of HU gene of Bifidobacterium longum, is disclosed in detail.

The instant invention is characterized by using a vector integrated with a HU gene promoter and terminator, and to express effectively the introduced gene. To clarify this feature

of the instant invention, claim 28 now limits the promoter and terminator to "a promoter and terminator involved in expressing a gene coding for a histone-like DNA binding protein belonging to the genus Bifidobacterium."

On the other hand, the cloning vector of Brown, is characterized by that a promoter of Fd gene has been introduced, as it is described in Example 3. There is no disclosure of a cloning vector in Yazawa.

Thus, there is no teaching neither in Brown or Yazawa, of a bacterium belonging to the genus Bifidobacterium transformed by a cloning vector having a HU gene promoter and terminator that can express effectively the introduced gene. Even by combining Brown and Yazawa, the instant invention cannot be achieved.

Accordingly, reconsideration and withdrawal of the 35 U.S.C. § 103 rejections are respectfully requested.

IV. REJECTIONS UNDER 35 U.S.C. § 112, 2ND PARAGRAPH, ARE OVERCOME

Claim 32 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action contends that the phrase "derived from Bifidobacterium Longum" is unclear.

Claim 32 is amended herein to clarify that the promoter and terminator are involved in expressing a gene encoding a histone-like DNA binding protein of Bifidobacterium longum. Further, the phrase "derived from Bifidobacterium Longum" is removed from the claim.

Reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph, rejection is respectfully requested.

V. REJECTIONS UNDER 35 U.S.C. § 112, 1ST PARAGRAPH, ARE OVERCOME

Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action asserts that the specification does not describe promoters and terminators "derived from Bifidobacterium Longum."

Applicants reiterate that the claim 32 is amended herein to recite that the promoters and terminators are "involved in expressing a gene encoding a histone-like DNA binding protein of

Bifidobacterium longum" and that the phrase "derived from Bifidobacterium Longum" is removed. This amendment is clearly supported in the specification, for example, on page 4, line 25 - page 5, line 9, and on page 7, lines 9-13.

Accordingly, reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
Deborah L. Lu
Reg. No. 50,940
Telephone: (212) 588-0800
Facsimile: (212) 588-0500